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PATENTS LAW, 5727-1967

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בקשה לפטנט  
Application for Patent

אני, (שם המבקש, מענו – ולגבי גופו מאוגד – מקום התאגדותו)  
I (Name and address of applicant, and, in case of a body corporate, place of incorporation)

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תכשירים למניעת ניוזן העור

(בעברית)  
(Hebrew)

PREPARATIONS FOR THE PREVENTION OF SKIN ATROPHY

(באנגלית)  
(English)

Inventor: Shabtay Dikstein

hereby apply for a patent to be granted to me in respect thereof.

המציא: שבתאי דיקשטיין  
מבקש בזאת כי ינתן לי עליה פטנט.

* בקשה חילוק Application for Division	* בקשה פטנט מוסף Application for Patent of Addition	* דרישת דין קידמה Priority Claim		
* מבקשת פטנט from Application	* לבקשת / לפטנט To Patent/App.	מספר/סימן Number/Mark	תאריך Date	מדינת האיחוד Convention Country
No. _____ Mat' _____ Dated _____	No. _____ Mat' _____ Dated _____			
* ימי כח: כללי/מיוחד - רצוף זהה / עוד יוגש P.O.A.: general / specific - attached / to be filed later				
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## תכשירים למניעת ניוזן העור

PREPARATIONS FOR THE PREVENTION OF SKIN ATROPHY

## FIELD OF THE INVENTION

The present invention relates generally to the field of topical preparations for skin treatment. More specifically, the present invention relates to topical preparations for treatment of skin aging and atrophy.

## BACKGROUND OF THE INVENTION

When women enter into postmenopausal age, their estrogen as well as their androgen production drops significantly. Testosterone production in premenopausal women is about 250 micrograms per day whereas in postmenopausal women it is about 100 micrograms per day. In comparison to this, male testosterone production is about 7 milligrams per day. It is now recognized that postmenopausal women can have good benefits from both androgen and estrogen supplements. There are available on the market pills for postmenopausal women that contain orally active androgen methyltestosterone in addition to the usual estrogen.

It is known that androgens applied locally to the skin can have certain benefits. Estrogens are ineffective to the skin whereas corticosteroids accentuated degradative changes (Papa, C.M. J. Soc.: Cosm. Chem. 18, 549, 1967). However, the challenge has been to find an androgen derivative that is active locally but without any systemic influence. The absorption of testosterone through the skin is known (in fact, certain testosterone-delivering patches, worn on the skin, are available). Thus, it would be desirable to have an androgen-containing preparation effective for diminishing the results of aging on the skin but without producing any side effects due to absorption into the bloodstream.

Surprisingly, androgen-containing topical preparations that decrease atrophy of the skin due to aging or external factors, such as photoaging, or prolonged corticosteroid treatment have been found. Specifically, it has been found that locally applied testosterone esters (especially testosterone phenyl propionate), in which the ester portion contains more than 5 carbons, provided excellent local skin activity at relatively low concentrations of 0.1-1%. At such low concentrations, the absorption into the bloodstream is substantially negligible. The topical preparations of the present invention have been shown to ameliorate the degradative changes of senescence or of external

factors such as photodamage or corticosteroid atrophy, with negligible absorption into the blood.

It is noted that aging of the skin is mainly a problem of the dermis and by legal definition, a cosmetic product should not affect the dermis.

#### SUMMARY OF THE INVENTION

The present invention relates to topical skin preparations for the use in the prevention of atrophy and aging of the skin, comprising a testosterone ester including an esterifying acid having between six to eleven carbon atoms provided that the topical preparation has no estrogen or estrogen derivatives.

Examples of estrogen derivatives that should not be included in the preparation of the invention are estradiol or its esters, estriol or its esters and the like.

According to preferred embodiments of the present invention, the testosterone ester is testosterone phenyl propionate. Preferably, the testosterone phenyl propionate is in a concentration of 0.1-1% by weight of the total preparation.

Further according to preferred embodiments of the present invention, the skin preparations are in the form of an oil solution. Preferably, the oil is a medium chain triglyceride.

Further according to preferred embodiments of the present invention the topical skin preparations may further include at least one additional therapeutically active agent, having no estrogenic activity. Examples of such agents are oil soluble vitamins or their derivatives such as vitamin A or retinoic acid, Vitamin D<sub>3</sub> or calcitriol, vitamin E, essential fatty acids or their esters.

The present invention also relates to a method for the treatment of atrophy or aging of the skin comprising administering to a patient in need of such treatment a topical skin preparation as described above.

#### DETAILED DESCRIPTION OF THE INVENTION

The following are meant to provide non-limiting examples for preferred embodiments of the topical skin preparations of the present invention.

##### Examples

Example 1: Oily Solution

Testosterone phenyl propionate 0.3% or 1% dissolved in medium chain triglycerides.

Suitable preservatives, antioxidants, and/or perfumes may also be added.

Example 2: Oily solution with vitamin E

The preparation of this solution was carried out as in Example 1 above with the addition of 2% vitamin E

Example 3: Oily solution with vitamin D

The preparation of this solution was carried out as in Example 1 above with the addition of 0.01% vitamin D<sub>3</sub>.

Example 4: Oily solution with Vitamin A

The preparation of this solution was carried out as in Example 1 above with the addition of 0.25% vitamin 'A<sub>1</sub>'.

Example 5: Testosterone Phenyl Propionate In an oil rich in Essential Fatty Acids

Testosterone phenyl propionate 0.1 to 1% dissolved in safflower oil

Human Studies:

Eight postmenopausal women were treated with the skin preparation of Example 1 daily for three months on the skin of the inner arm. Biopsies were taken from the treated skin and from adjacent non-treated skin. The biopsies were evaluated and described according to the criteria described in Timar, F. et al. Skin Res. Technol. 6, 17, 2000). The results are given in Table 1 below.

TABLE 1

Name	Epidermal		Dermal	
	Thickness (microns)	Cell Layers	Interdigitation Index	Amount of GAG (%)
Changes from Control (data)				
TP 1	$8.7 \pm 1.5$ (*)	$0.18 \pm 0.37$	$0.22 \pm 0.07$ (*)	$2.7 \pm 0.8$ (*)
TP 0.3	$0.3 \pm 5.7$	$-0.2 \pm 0.45$	$0.07 \pm 0.04$	$2.2 \pm 1.3$

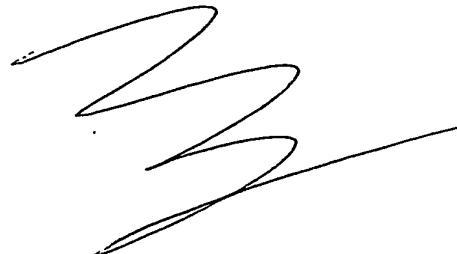
GAG= glucose amino glycan

TP= Testosterone phenyl propionate

\* = significantly different from normal old cohort

## CLAIMS

1. Topical skin preparations for the use in the prevention of atrophy and aging of the skin, comprising a testosterone ester with an esterifying acid having between six to eleven carbon atoms, provided that the topical preparation does not comprise estrogen or estrogen derivatives..
2. Topical skin preparations according to claim 1, wherein the testosterone ester is testosterone phenyl propionate.
3. Topical skin preparations according to claim 2, wherein the testosterone phenyl propionate is in a concentration of 0.1-1% by weight of the total preparation.
4. Topical skin preparations according to claim 3, in the form of an oil solution.
5. Topical skin preparations according to claim 4, wherein the oil is a medium chain triglyceride.
6. Topical skin preparations according to any one of claims 1-5, further comprising at least one additional therapeutically active agent. .
7. Topical skin preparations according to claim 6 wherein the additional therapeutic agent is selected from the group consisting of: vitamin A , retinoic acid, vitamin D<sub>3</sub>, calcitriol,, vitamin E, essential fatty acid, essential fatty acid ester, or a combination of at least two of the above agents
8. A method for the treatment of atrophy or aging of the skin comprising administering to a patient in need of such treatment a topical skin preparation as described in any one of claims 1-7.

A handwritten signature in black ink, appearing to read "J. R. HARRIS".